NATIONAL CANCER INSTITUTE

2011 Radiation Epidemiology and Dosimetry Course

ACUTE (EARLY RESPONSE) BIOLOGICAL DOSIMETRY

William F. Blakely, Ph.D.

Biological Dosimetry Research Group Advisor
Armed Forces Radiobiology Research Institute,
Bethesda, Maryland, USA
On-line CV: myprofile.cos.com/wfblakely
Email: blakely@afrri.usuhs.mil

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Financial Interest, Other Relationships Disclosure, and Disclaimer

Commercial Manufacturer	Financial Interest	Other Relationship
BioRad, Careside	None	Equipment evaluation
Various companies developing 1st responder software applications	None	Interactions with Technical Support Working Group developers
Meso Scale Diagnostics	None	Co-Investigator on BARDA contract to develop radiation responsive biomarker device for radiation dose assessment

Patent Title	Status
Biomarker Panels For Assessing Radiation Injury And Exposure	U.S. patent application filed 6-12-08; WH 2001797.121 PCT/US2007/013752
A simple and rapid method to induce premature chromosome condensation in human resting peripheral blood lymphocytes, to study structural and numerical chromosomal aberrations involving specific chromosomes	Patent Number: Provisional patent, 2001, International PCT application filed. Institution-owned, United States of America.
Mouse genomic DNA hybridization probe an immunoenzymatic color pigment detection of mouse bone marrow micronucleus for regulatory required genetic toxicity assay (mouse bone marrow micronucleus assay)	Patent Number: Provisional patent filed, 2000, Institution-owned, United States of America.

The views expressed here are those of the authors; no endorsement by the U.S. Department of Defense has been given or inferred.

Lecture Objectives/Outline*

- Review scenarios when biological dosimetry is used in suspected or known radiation exposures.
- Review and illustrate the use of clinical symptoms and hematology to assess radiation exposure.
- Review and illustrate the use of cytogenetic biodosimetry for dose assessment.
- Describe applications of molecular biomarkers in radiation accidents as well as current research efforts to enhance this capability.

*Retrospective biological dosimetry was addressed by Dr. James Tucker's lecture on Wednesday May 18, 2011. Additional information can be found in manuscript by Dr. Steve L. Simon and colleagues entitled Current use and future needs of biodosimetry in studies of long-term health risk following radiation exposure, Health Phys. 2010 Feb;98(2):109-17.

Conditions Where Bioindicators of Radiation Exposure Would be Useful

- **Exposures of personal dosimeters**
  Accidental contamination of personal dosimeter

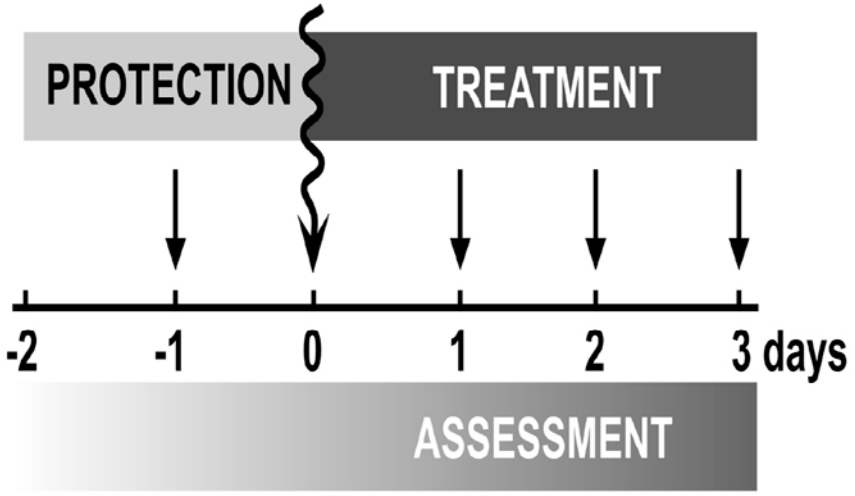
- **Suspicion of receiving higher or lower dose than indicated by the dosimeter**
  - **Doubtful about wearing the dosimeter**

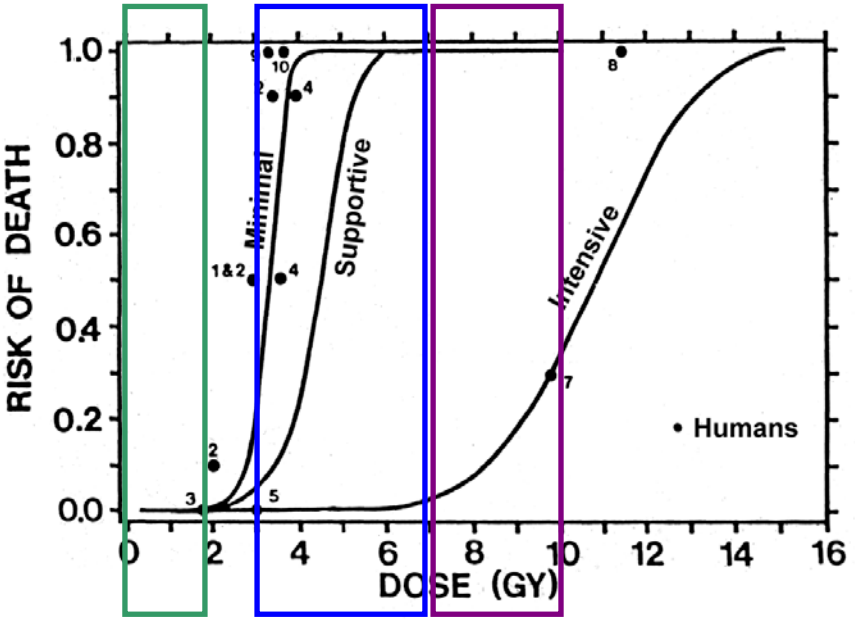
- **Unusual radiation exposure of individuals not belonging to the atomic radiation worker group**

- **Accidental or emergency exposure**

- **Exposures of occupationally exposed persons under unusual circumstances**
  - **An exposure above an applicable dose limit**
  - **Medical assessment**

Early-Response Biological Dosimetry





Mass Casualty Incident, healthy individual with no other injuries:

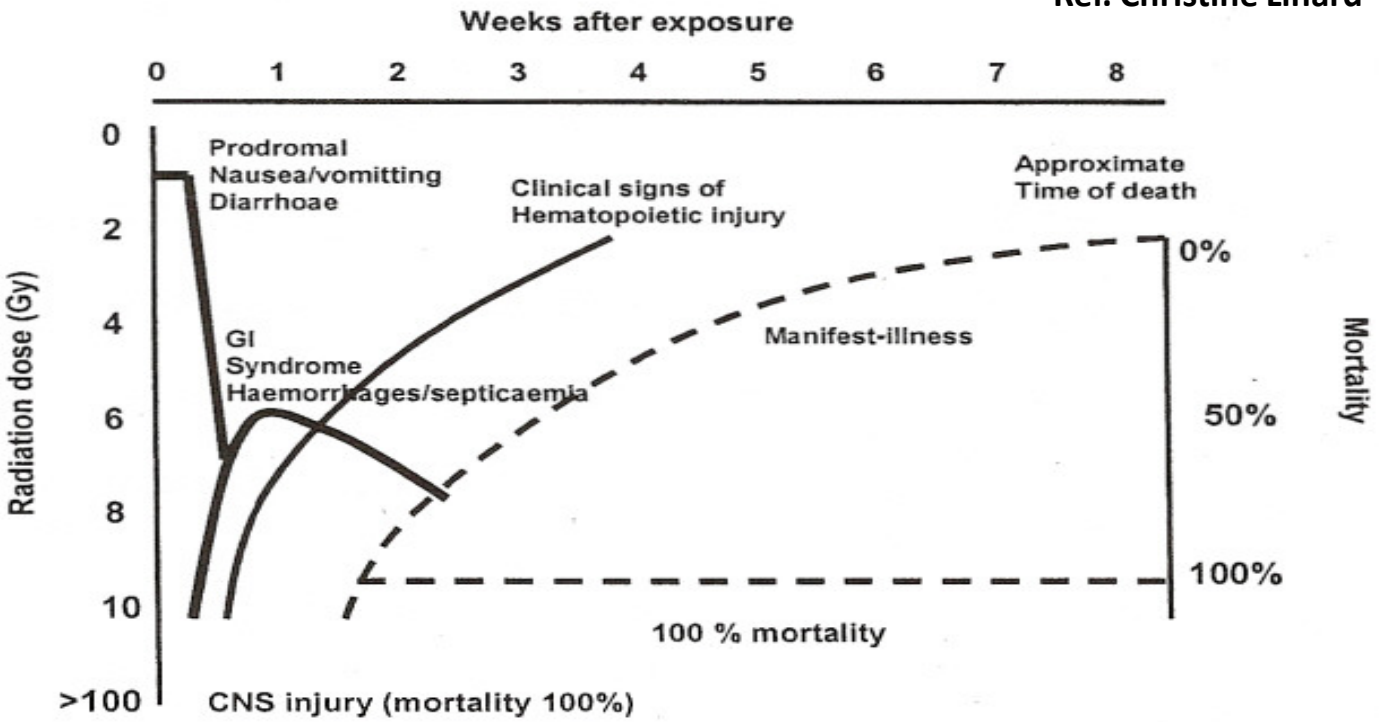
- **Identify "concerned public" (worried well)**
- **Identify candidates for cytokine therapy (i.e., filgrastrim) as soon as possible after exposure (20 h)**
- **Identify candidates for stem-cell transplant therapy**

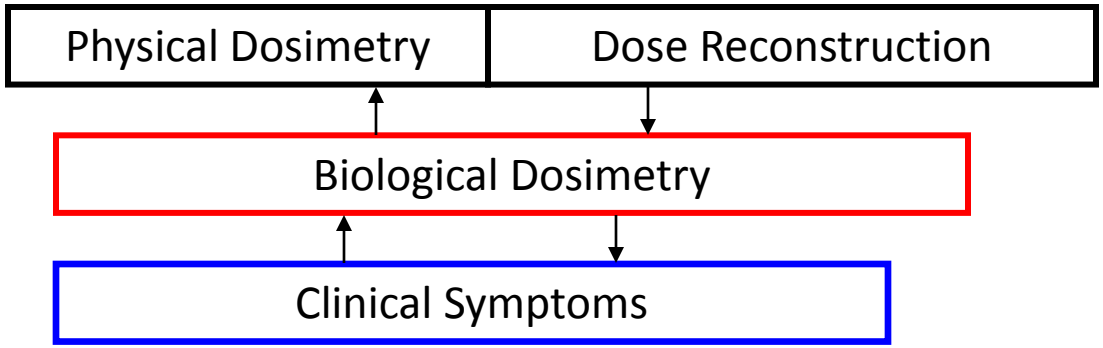
Waselenko JK, MacVittie TJ, Blakely WF, et al. (2004) Medical management of the acute radiation syndrome: recommendations of the Strategic National Stockpile Radiation Working Group. *Ann Intern Med*. 140(12):1037–1051.

Blakely WF (2008) Early Biodosimetry Response: Recommendations for Mass-Casualty Radiation Accidents and Terrorism. Refresher Course for the 12th International Congress of the International Radiation Protection Association, October 19–24, 2008, Buenos Aires, Argentina, accessible at website: http://www.irpa12.org.ar/PDF/RC/_12_fullpaper.pdf

Acute Radiation Syndromes

Ref. Christine Linard

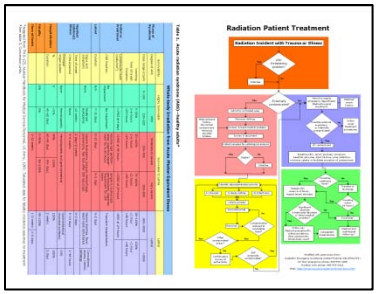


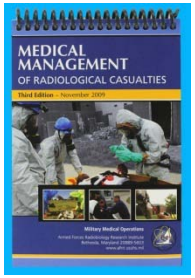


Products/Radiation Biological Dosimetry Tools for Emergency Responders

Casualty management guidance

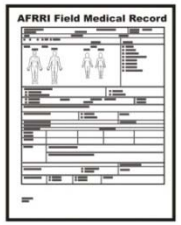
- Pocket guide to emergency procedures
- Handbook on medical management of radiological casualties
- Quick Reference Information (NCRP Recommendations)
- Internal Contamination

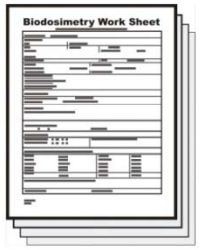


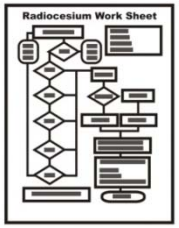


Medical data forms

- One-page emergency medical record
- Six-page radiation exposure worksheet
- One-page radiocesium worksheet

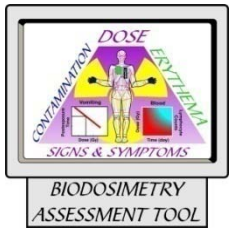






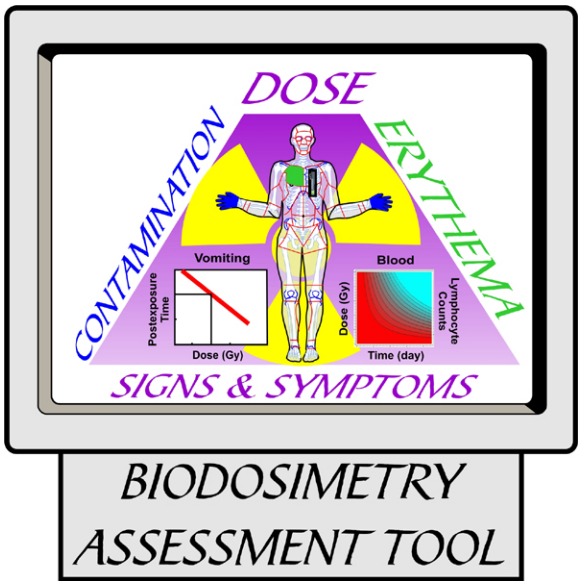
Exposure assessment software

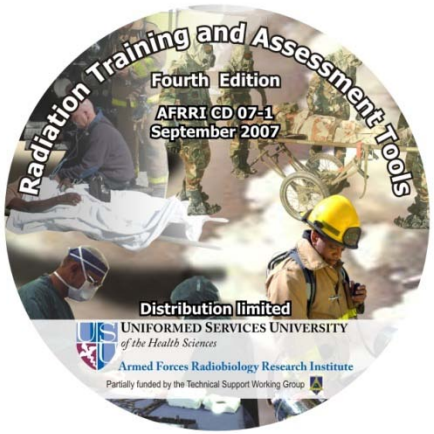
- Data-entry generated recording and diagnostic tools
  - Biodosimetry Assessment Tool (BAT)
  - First-responder Radiological Triage (FRAT)



AFRRI Website: www.afrri.usuhs.mil

Software Program for Collection of Radiation Exposure Medical Data





- **Interprets dose-related diagnostic signs and records blood cell counts and other indices of exposure**
- **All file stored on local hard drive**
- **BAT and other products available at AFRRI website http://www.afrri.usuhs.mil**

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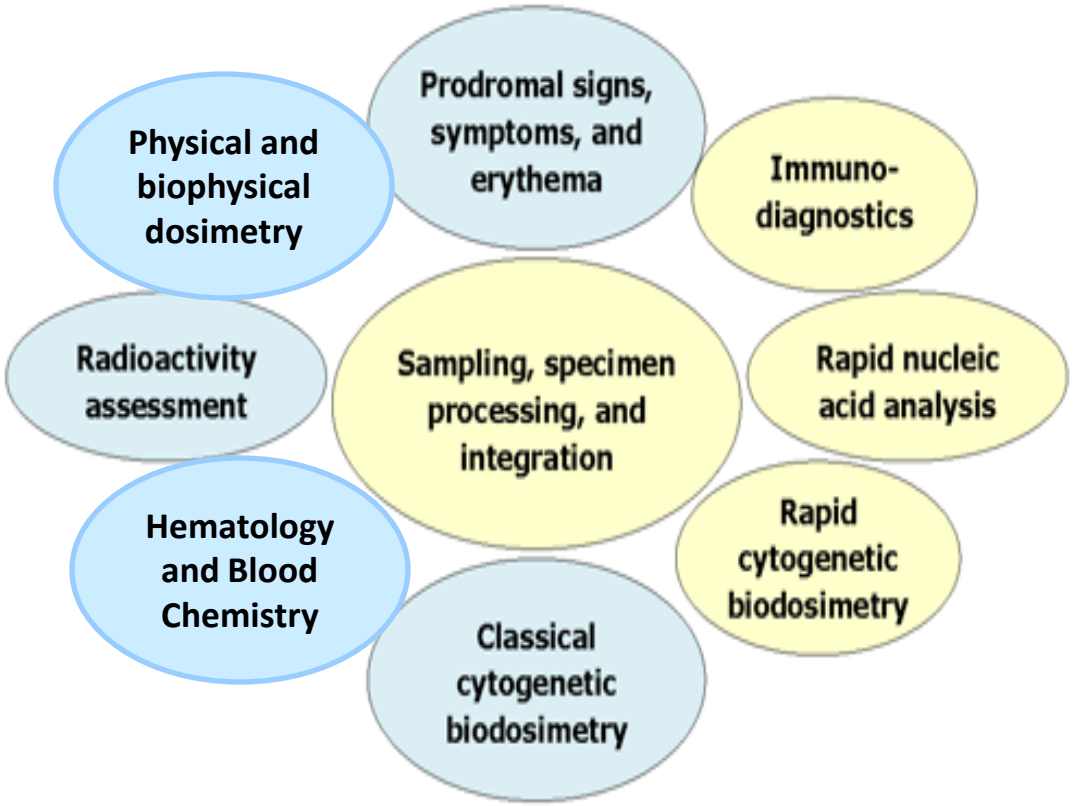
Biodosimetry — General Guidance

Actions needed in suspected overexposures:

- Perform measurement and bioassay, if appropriate, to determine radionuclide contamination
- Record physical dosimetry measurements, if available
- Observe/record prodromal signs (erythema), symptoms, and clinical bioassays
- Obtain CBC with white blood cell differential immediately, then every 6 hours for 2-3 days, and then twice a day for 4 days
- Contact qualified laboratory to evaluate performance of chromosome-aberration cytogenetic bioassay, using the “gold standard” dicentric assay for dose assessment
- Consider other opportunistic dosimetry approaches as available

Blakely WF, Salter CA, Prasanna PG. Early-response biological dosimetry — recommended countermeasure enhancements for mass-casualty radiological incidents and terrorism. Health Physics 89(5):494–504, 2005.
Waselenko JK, MacVittie TJ, Blakely WF, et al. Medical management of the acute radiation syndrome: recommendations of the Strategic National Stockpile Radiation Working Group. *Ann Intern Med*. 140(12):1037–1051, 2004.

Integrated Biodosimetry and Diagnostic Systems

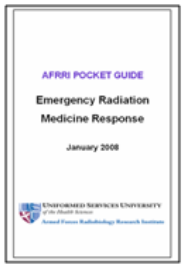


✓No single assay is sufficient to address potential radiation exposure scenarios that are complex and involve mass casualties.

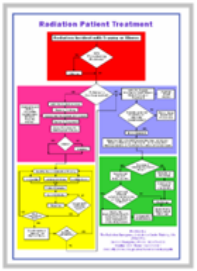
✓Triage, clinical, and definitive radiation biodosimetry all require multiple bioassays and analytic technologies designed for use in chemical, biological, radiological, and environmental (CBRE) diagnostics and general medical care.

General Hypothesis. The use of multiple parameter biodosimetry assessment based on measurement of hematology changes, blood enzyme activities and/or proteins will enhance early diagnostic triage for acute radiation exposures.

Biodosimetry Concept of Operations – Medical Recording



Radiation Patient Assessment Algorithm – Medical Recording



Access and Stabilize Life Threatening Problems

Externally Contaminted?

Yes

No

No

Medical Recording:
- Radiation Survey
- Radiobioassay Sampling

Initial Decontamination, Access and Treat Life-Threatening Medical Problems, and Stabilize Patient

Initial Radiation Exposure Assessment

Medical Recording:
- Clinical Signs & Symptoms
- Haematology
- Blood Chemistries
- Radiobioassay Sampling
- Alternate Radiation Screening Assessment Assays

Medical Recording:
- Radiation Survey
- Radiobioassay Sampling

Prioritize Decontamination and Decontaminate

Follow-up Radiation Exposure Assessment

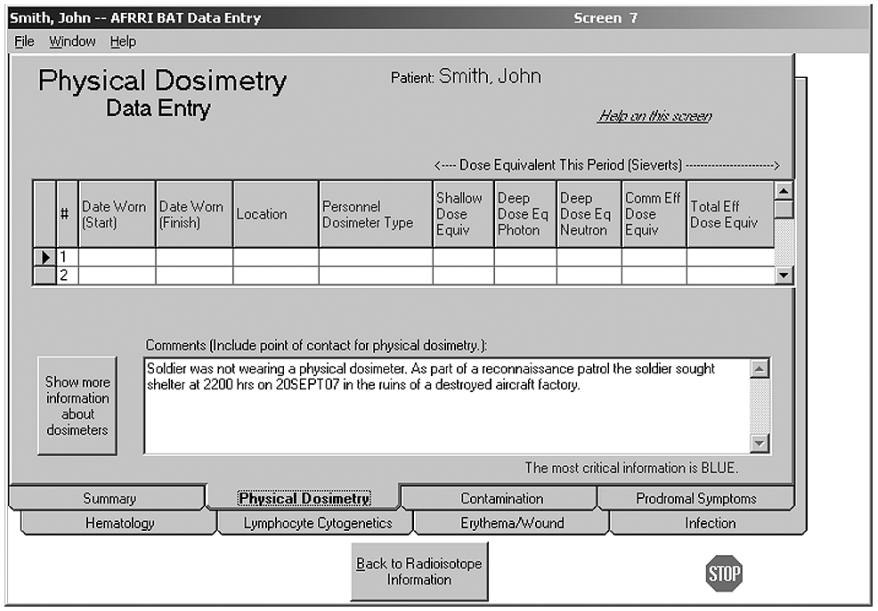
Medical Recording:
- Clinical Signs & Symptoms
- Haematology
- Blood Chemistries
- Radiobioassay Sampling
- Cytogenetic Biodosimetry
- Alternate Radiation Assessment Assays

Blakely et al. Health Physics 99 (suppl 3): S184-S191, 2010

General Guidance – Suspected Internal Radionuclide Contamination*

- Radioactivity decontamination to minimize local dose to potential wound site
- Metallic (or other) fragment sample collection for isotope identification
- Biological sample collection (e,g., urinalysis, fecal, wound, swipes from body orifices) for determination of committed dose

***Recommendations of Radiation/Nuclear Technology Countermeasures (RNTC) Working Group (WG) and Biodosimetry and Devices Subpanel**



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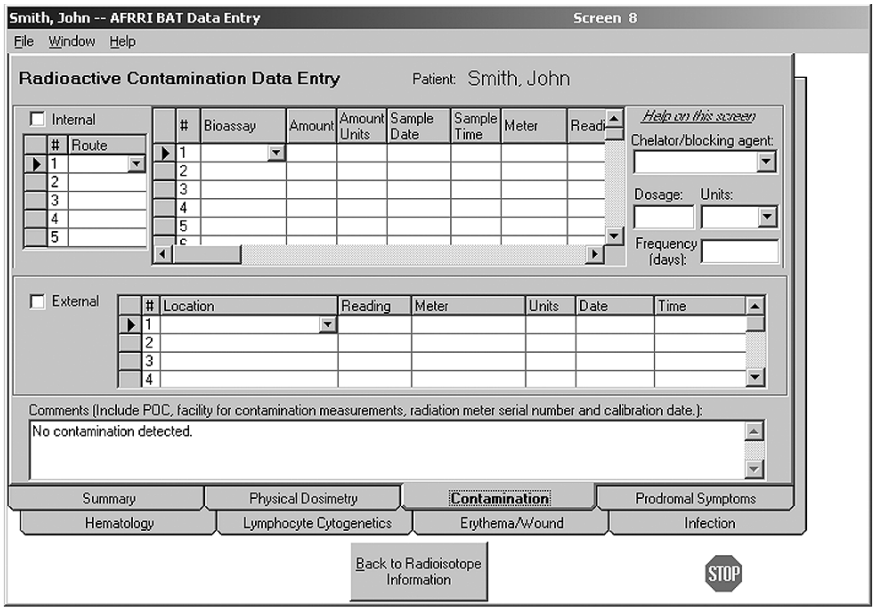

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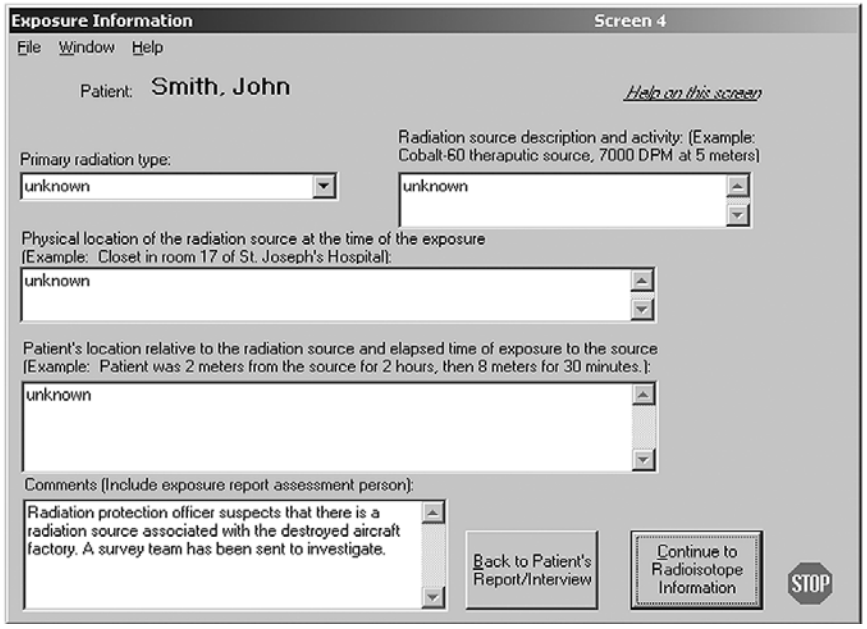

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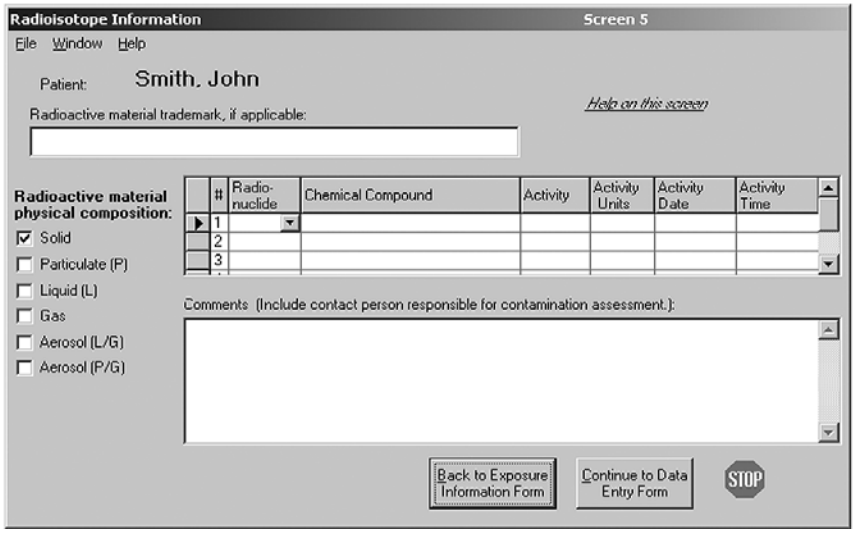

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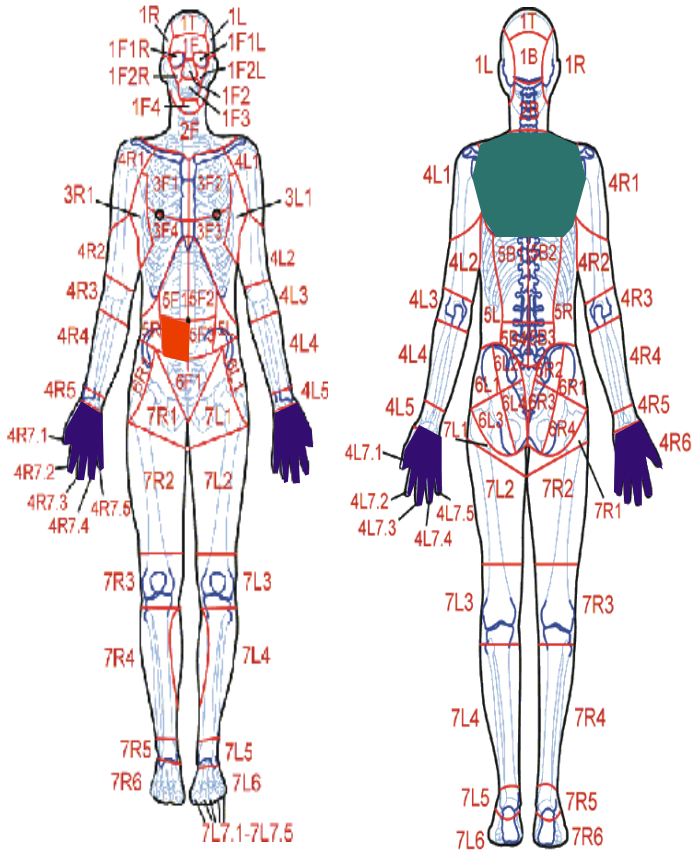
Blakely et al. Health Physics 99 (suppl 3): S184-S191, 2010

Anatomical Location



- **PHYSICAL DOSIMETRY**
  - **Location worn on body**
  - **Date of dosimeter exposure**
  - **Dosimeter type**
  - **Range, sensitivity**
  - **Reading, units**
- **ERYTHEMA**
  - **Location of erythema**
  - **Degree (mild, moderate, severe)**
- **RADIOACTIVE CONTAMINATION/ WOUND**
  - **Location of contamination (with or without wounds)**
  - **Radionuclide**
  - **Type of wound (abrasion, burn, laceration)**
  - **Survey instrument selection list**
  - **Survey reading (counting) entry with sequential time measurements**

User clicks on affected region, which is automatically entered in the "location" section of the appropriate data entry table.

Acute Radiation Syndromes - Phases

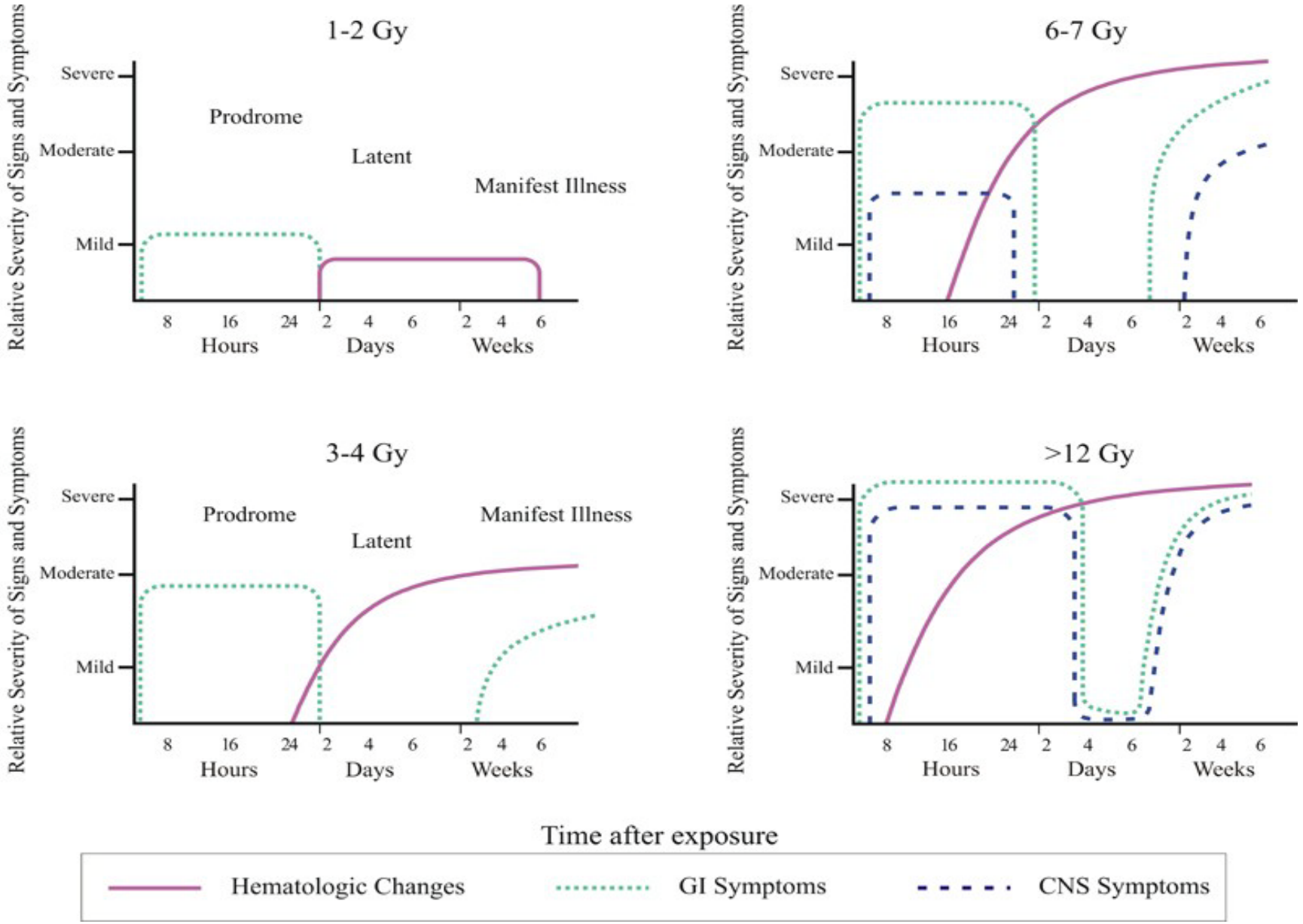


Table II.A.3 Prodromal phase of acute radiation syndrome

Doses	1-2 GyEq	2-4 GyEq	4-6 GyEq	6-8 GyEq	>8 GyEq
Vomiting					
(Onset)	after 2 h	1-2 h	within 1 h	within 30 min	within 10 min
(%)	10-50	70-90	100	100	100
Diarrhea			moderate	severe	severe
(Onset)	-	-	3-8 h	1-3 h	<1 h
(%)	-	-	<10	>10	100
Headache	slight	mild	moderate	severe	severe
(Onset)	-	-	4-24 h	3-4 h	1-2 h
(%)	-	-	50	80	80-90
Consciousness	unaffected	unaffected	unaffected	may be altered	unconsciousness
(%)	-	-	-	-	100 (>50 Gy)
Body temperature	normal	increased	fever	high fever	high fever
(Onset)	-	1-3 h	1-2 h	<1 h	<1 h
(%)	-	10-80	80-100	100	100

Cited from the IAEA Safety Reports Series No. 2 (IA98) and modified. The doses are mainly gamma ray doses at the time of exposure.

MEIR, Scenario, 1 -- AFRRI BAT Data Entry Screen 9

File Window Help

Prodromal Symptoms
Data Entry

Patient: MEIR, Scenario, 1

Help on this screen

Check all that apply:

The most critical information is BLUE.

- [x] Nausea
- [x] Vomiting
- [ ] Antiemesis therapy administered prior to initial vomiting

Start of initial vomiting:

Date: 9/21/2007

Time: 05:00

Obtain Dose Assessment

IF THE PATIENT HAS CHANGED TIME ZONES SINCE EXPOSURE, provide the number of hours that elapsed from the time of exposure to the onset of vomiting:

Rate the severity of vomiting on a scale of 0 (almost none) to 10 (most severe): 2

- [x] Diarrhea
- [ ] Tachycardia
- [x] Fatigue
- [ ] Weakness
- [ ] Abdominal pain
- [ ] Headache
- [ ] Fever
- [x] Body temperature measured

#	Date	Time	Method	Temp. (° C)
1	9/22/2006	12:00	Rectal	37.00
2				
3				
4				

Comments (Click here to view or edit):

Vomiting initiated at 0500 on Sept. 21, 2007. He has had 3 episodes of

Summary | Physical Dosimetry | Contamination | **Prodromal Symptoms**

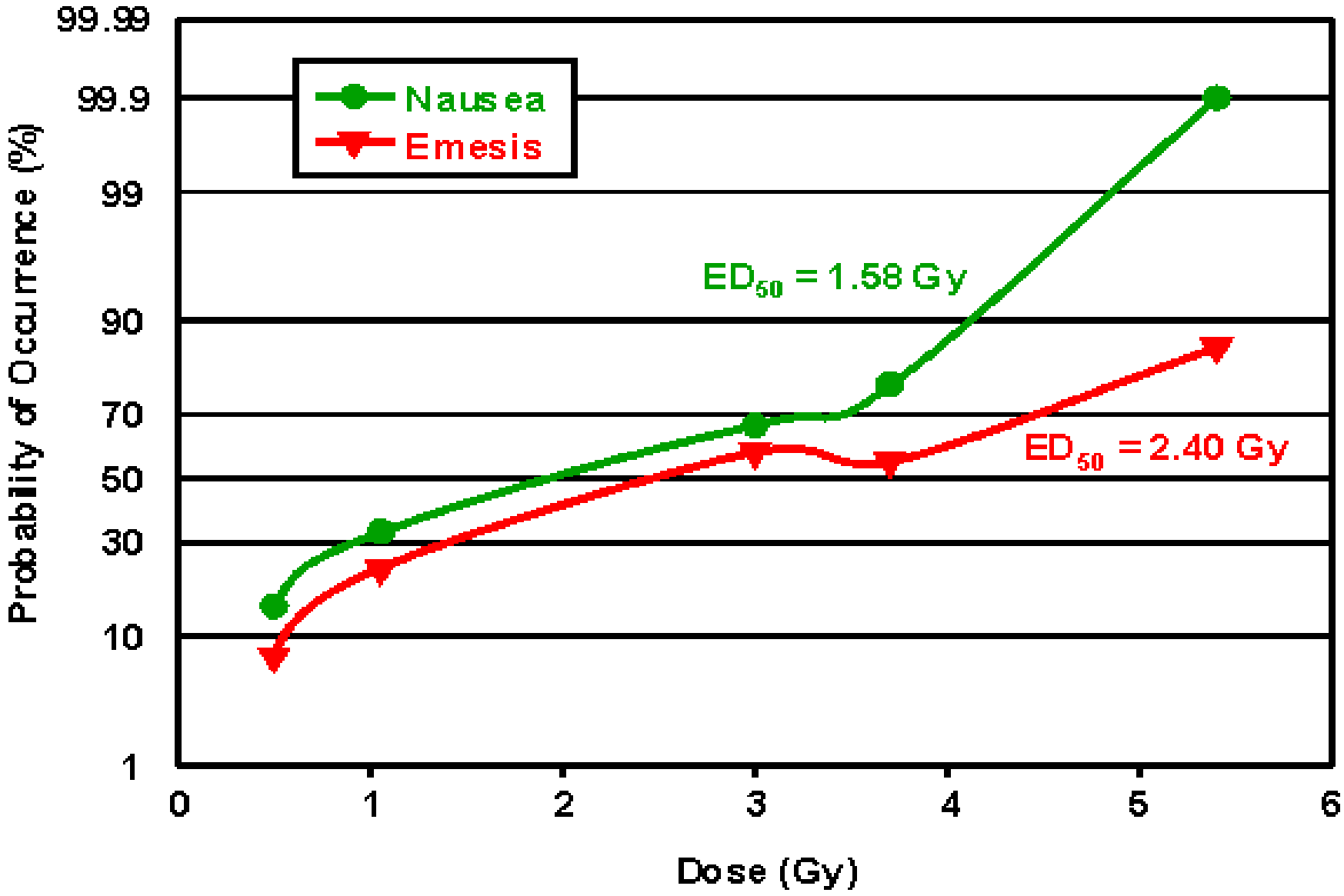
Hematology | Lymphocyte Cytogenetics | Erythema/Wound | Infection

Back to Radioisotope Information

STOP

Per Cent of Patients Who Vomit After Exposure

ORAU Low-Dose Experiments 1964-1975



Vomiting induced by exposure to ionizing radiation vomits occurs in a fraction of exposed humans (Goans *et al.*, in press).

Onset of Vomiting

BIODOSIMETRY ASSESSMENT TOOL

☑ Vomiting ☐ Antiemesis therapy administered prior to initial vomiting

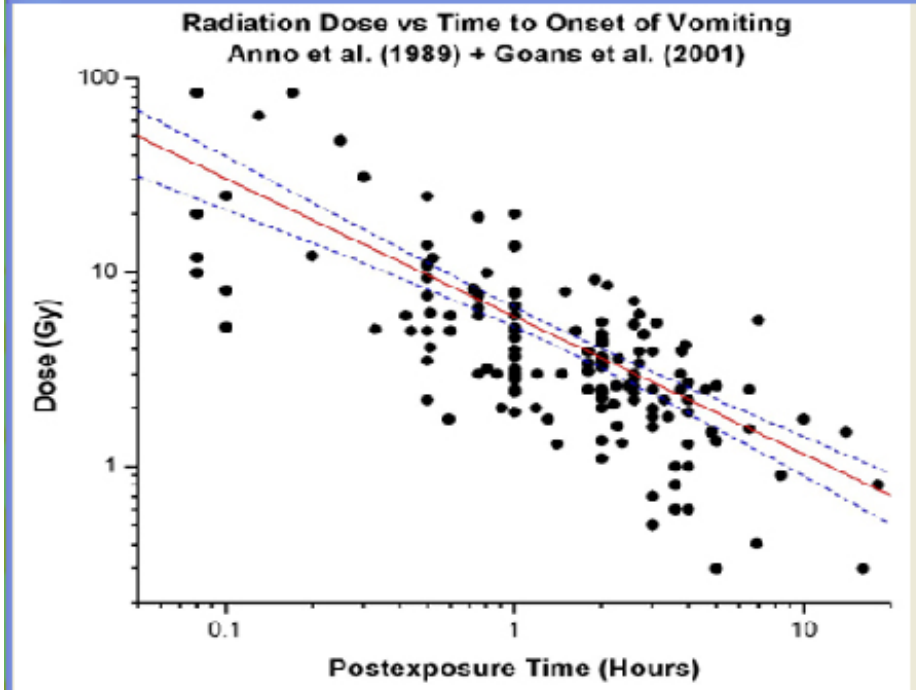
Start of initial vomiting:
Date: 9/21/2007
Time: 05:00

Obtain Dose Assessment

IF THE PATIENT HAS CHANGED TIME ZONES SINCE EXPOSURE, provide the number of hours that elapsed from the time of exposure to the onset of vomiting:

Rate the severity of vomiting on a scale of 0 (almost none) to 10 (most severe): 2

Obtain Dose Estimate from Emesis



Print this form

Time from exposure to onset of vomiting: 7.00 Hours

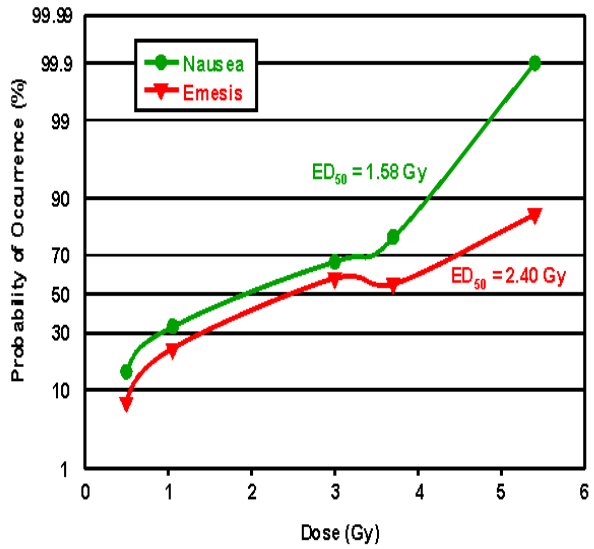
Estimated dose at time of exposure: 1.5 Gray (Gy)

95% CL (Gy): 1.1-1.9

Patient: MEIR, Scenario, 1

Anno, G.H., et al., Symptomatology of acute radiation effects in humans after exposure to doses of 0.5-30 Gy (Health Physics, Vol 56(6): 821-838, 1989). Dose rates ranged from very high (accident cases) down to 0.3 Gy/min (radiotherapy patients). Goans, RE, Clinical care of the radiation accident patient: patient presentation, assessment, and initial diagnosis (Found in: The Medical Basis for Radiation Accident Preparedness: The Clinical Care of Victim, Proceedings of the 4th International REAC/TS, Orlando, FL, March, 2001, Editors: Robert C. Ricks, Mary Ellen Berger, and Frederick M. Ohara, Jr., The Parthenon Publishing, Boca Raton, FL, 2001.). In general, midline doses are quoted. Confidence limits (dashed blue line) represent one SE from the fitted line (solid red).

Return to Data Entry



Vomiting induced by exposure to ionizing radiation vomits occurs in a fraction of exposed humans (Goans *et al.*, in press).

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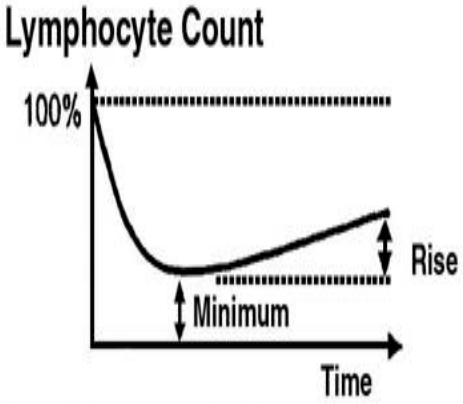
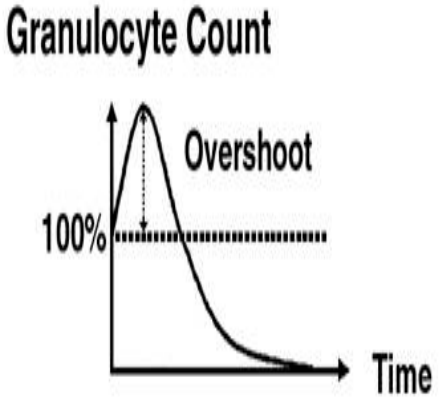
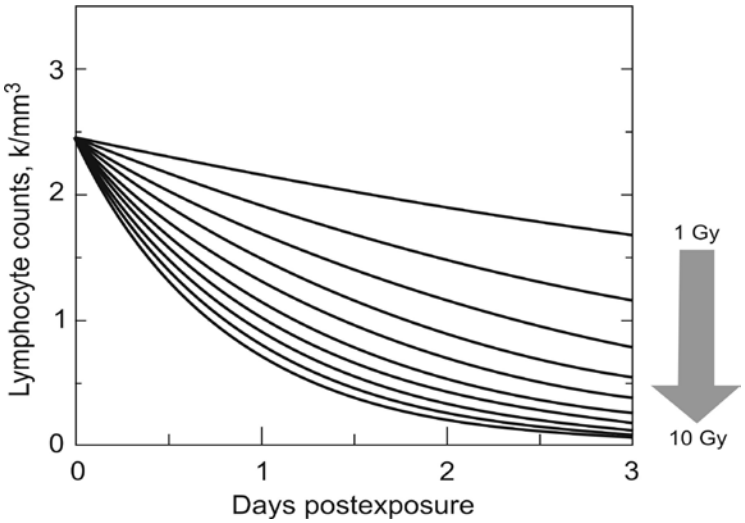
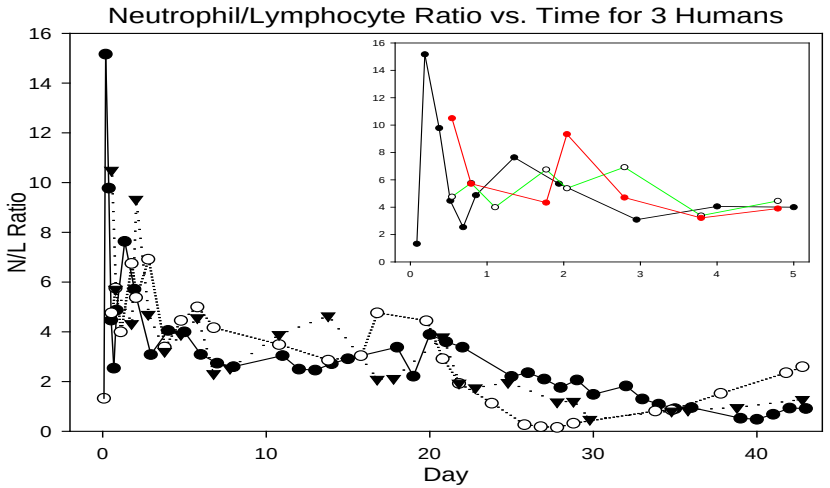
Hematological Biomarkers of Radiation Exposure



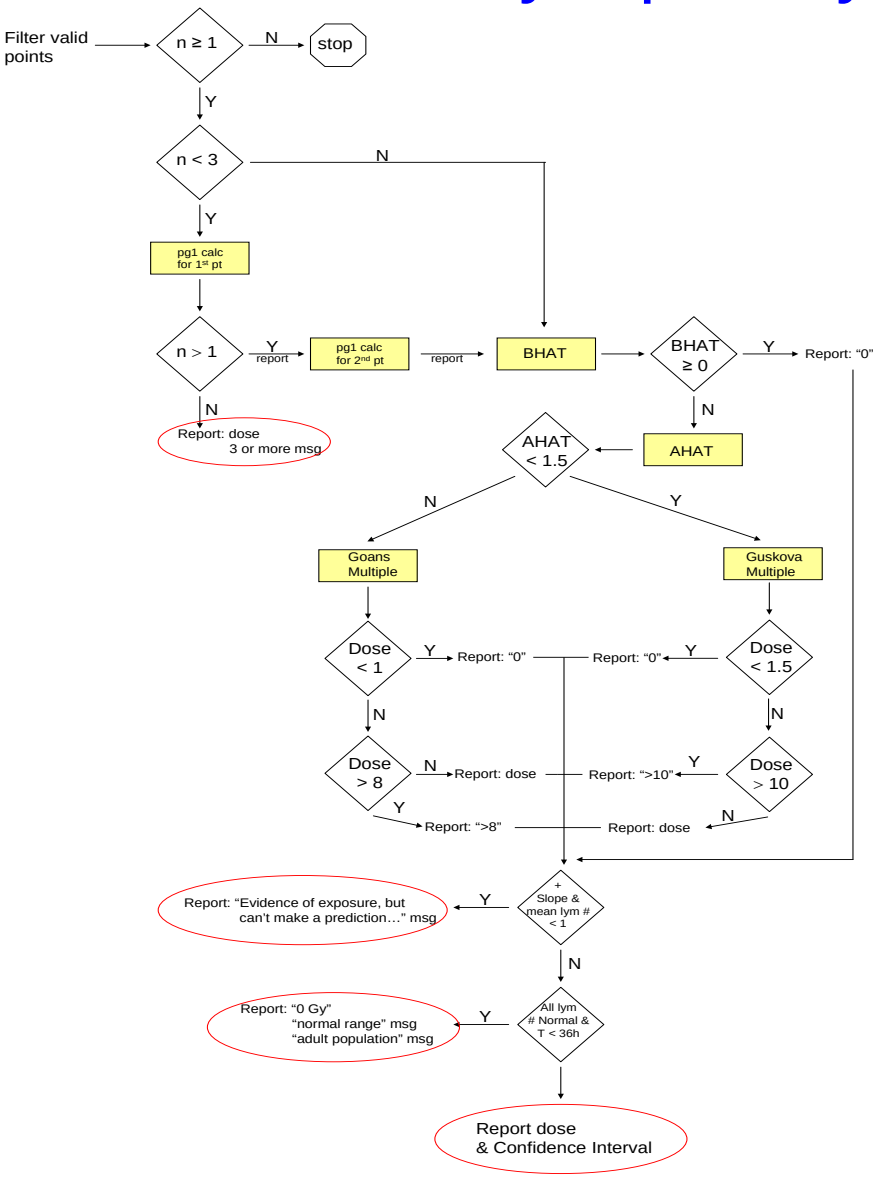


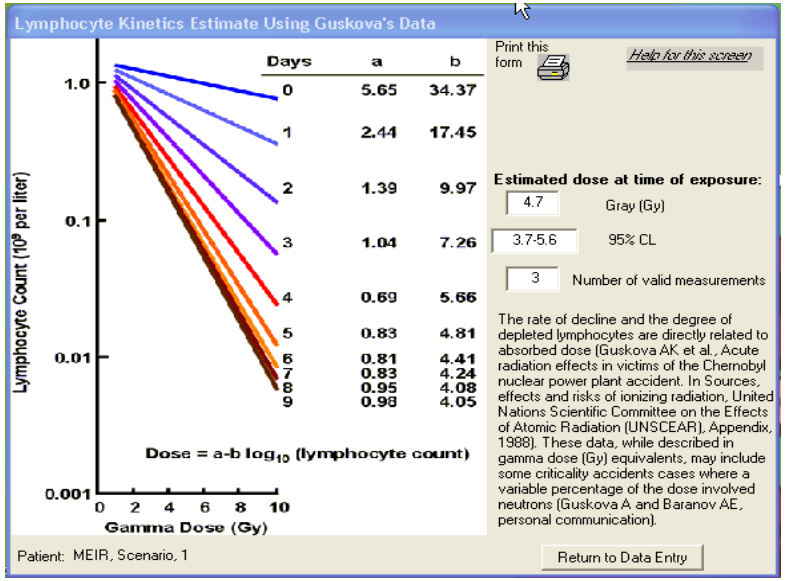
Ratio of neutrophils to lymphocytes proposed as an early biomarker of ARS (Zhang, Wald, and Day, 2005)

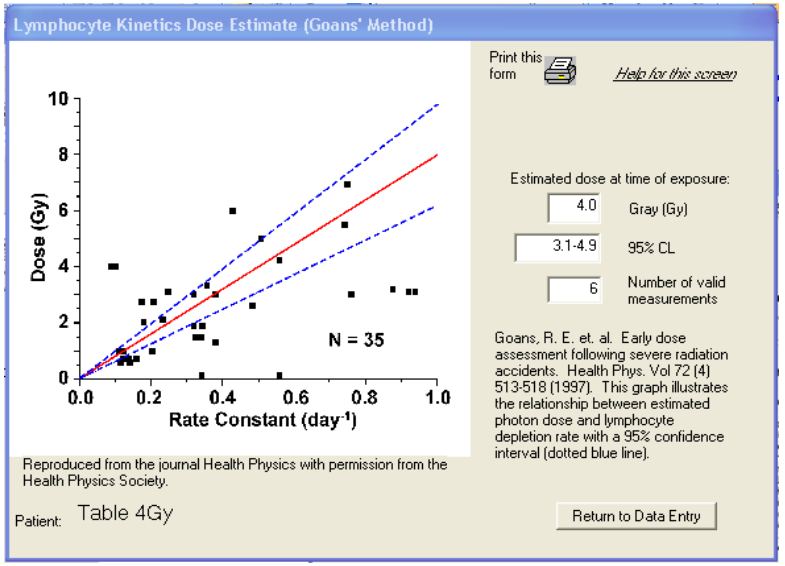




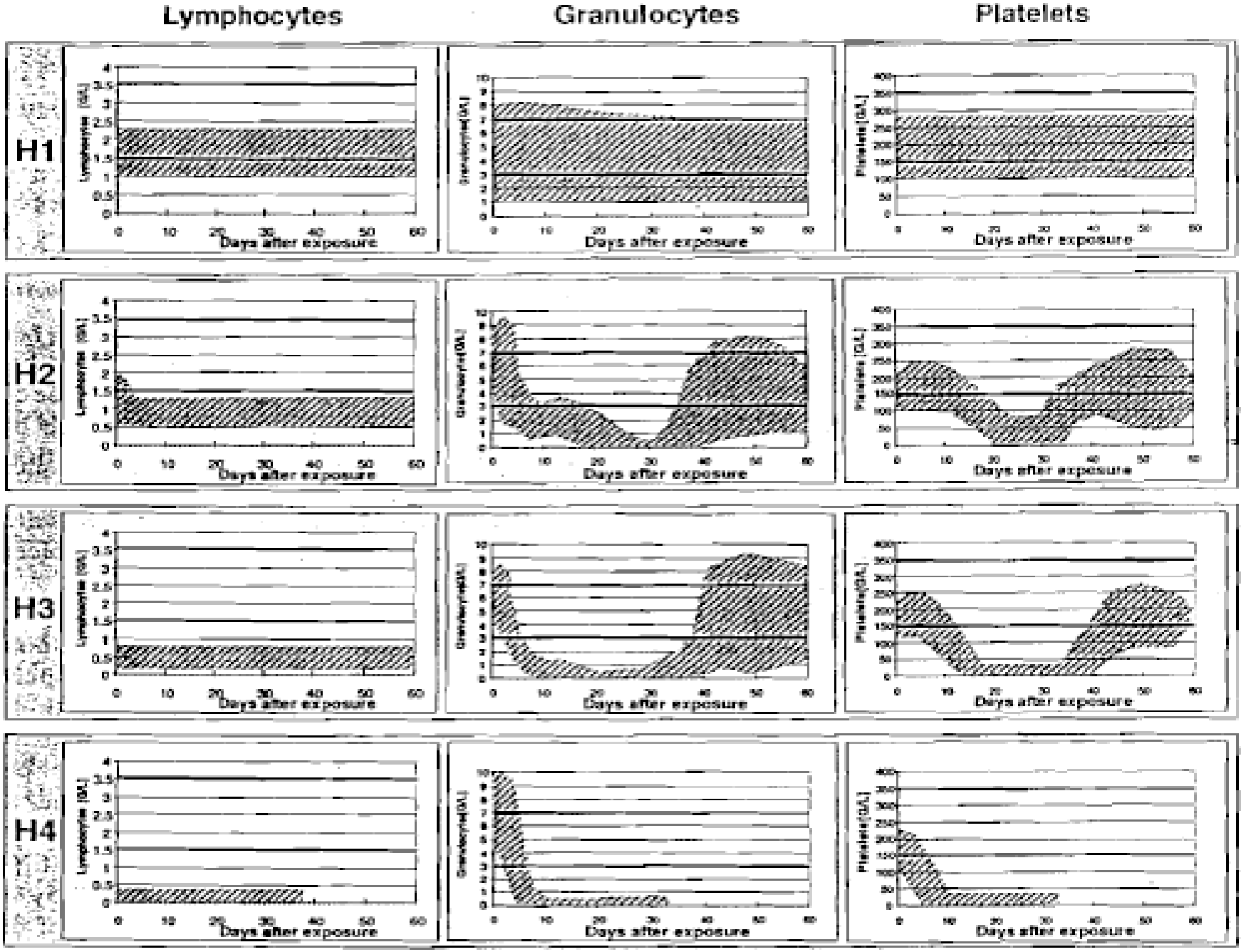
Dose Predictions Based on Lymphocyte Counts or Lymphocyte Depletion Kinetics







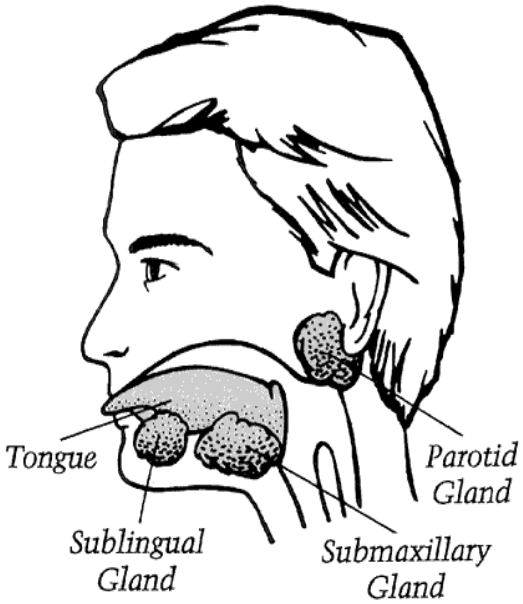
Sandgren et al. Health Physics 99 (suppl 3): S171-S183, 2010



Medical Management of Radiation Accident, Manual on the Acute Radiation Syndromes, The British Institute of Radiobiology, 2001

Radiation Sensitivity of Human Salivary Glands

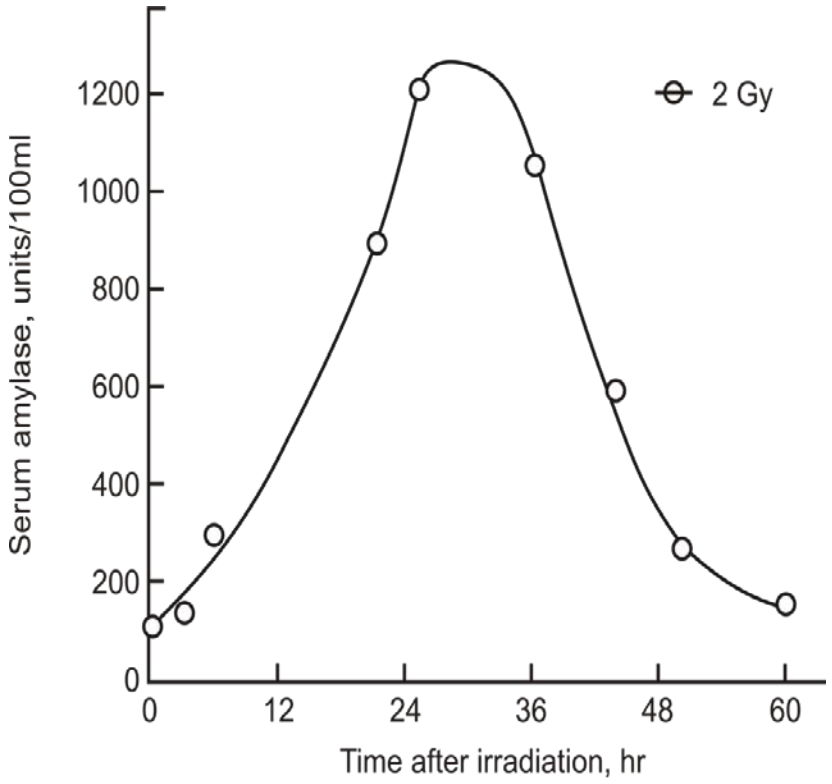
- The major salivary glands are the parotid, submandibular (submaxillary), and sublingual glands. Besides these glands, there are many tiny glands called minor salivary glands located in your lips, inner cheek area (buccal mucosa), and extensively in other linings of your mouth and throat.



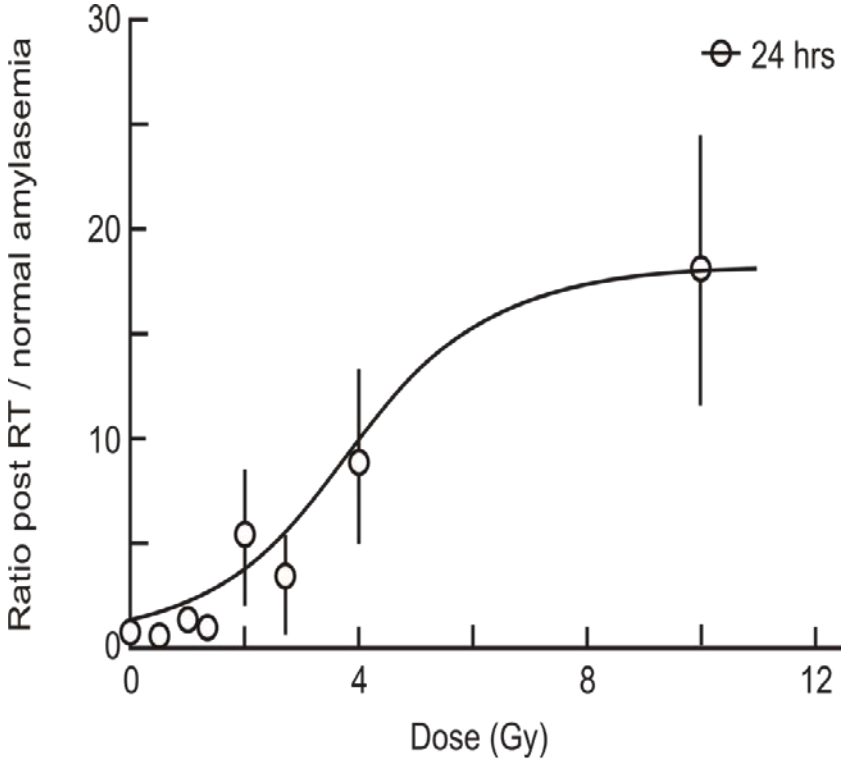
- The parotid seems to be more sensitive to irradiation than the submandibular gland (Henriksson et al., Brit. J. Cancer 69(2): 320-6, 1994).
- The post-irradiation induced proliferative activity was higher in the intercalated duct compartment of the parotid gland than of the submandibular gland, which may be related to the increased radiosensitivity (Peter et al., Radiat. Res. 140(2): 257-65, 1994).

- Nagler suggested that the causes for the specific parotid radiosensitivity are transition, highly redox-active metal ions, such as Fe and Cu, associated with secretion granules (Nagler, In Vivo 17(4): 369-75, 2003).

Use of Salivary Amylase Levels in Blood as a Biodosimeter Salivary Amylase Activity Levels in Human Serum Irradiation



Chen et al., Radiation Research 54, 141-151 (1973)

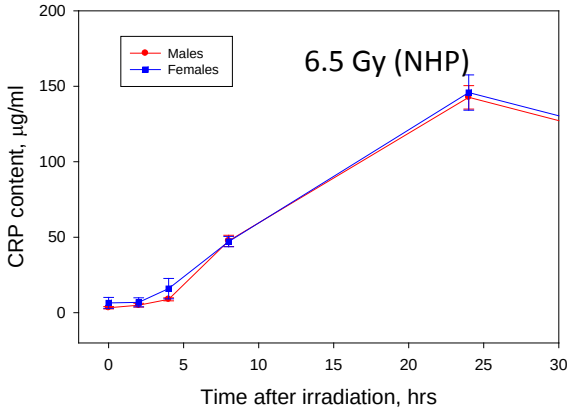


Dubray et al., Radiother Oncol 24(1), 21 (1992)

Radiological Triage Concept Using CRP

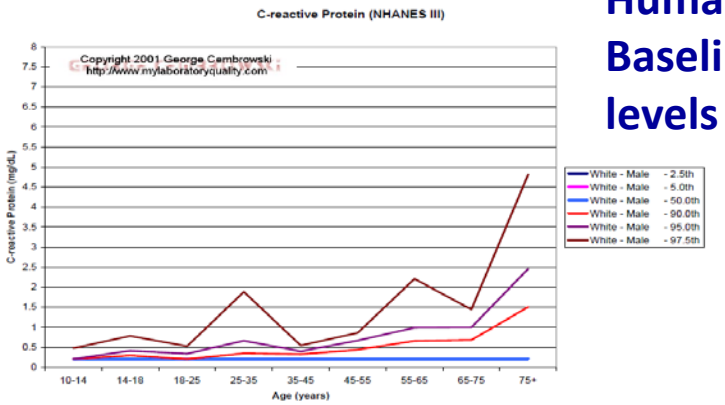
(Ossetrova and Blakely)

Rapid FDA Approved Devices

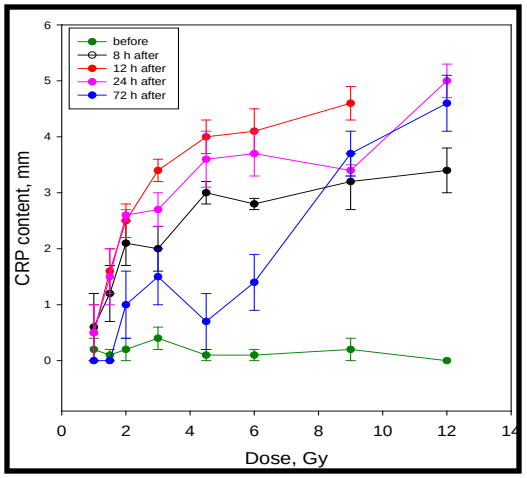


High signal to noise

Blakely *et al*., Health Physics, FEB 2010



Human Baseline levels



Biodosimeter

Maltsev *et al*., [Report of Russian Academia of Sciences] 239(3): 750-2, 1978 (in Russian).

ARS Bioindicator

Prognosis for ARS based on CRP level in serum of blood of people damaged at Chernobyl NPP accident during primary reaction (3-9 days after irradiation).

Degree of ARS	CRP level ≥ 1 mm	CRP level: 0.5 mm	CRP level 0 mm	Total (row)
3-4	26	9	17	52
2	6	7	19	32
0-1	3	18	23	44
Total (column)	35	34	59	128

Mal'tsev VN *et al*. [The individual prognosis of the gravity and of the outcome of radiation disease on immunological indexes], Radiation Biology. Radioecology, 46(2), 152-158, 2006 (in Russian).

Table I. Acute-phase patient assessment methods.*

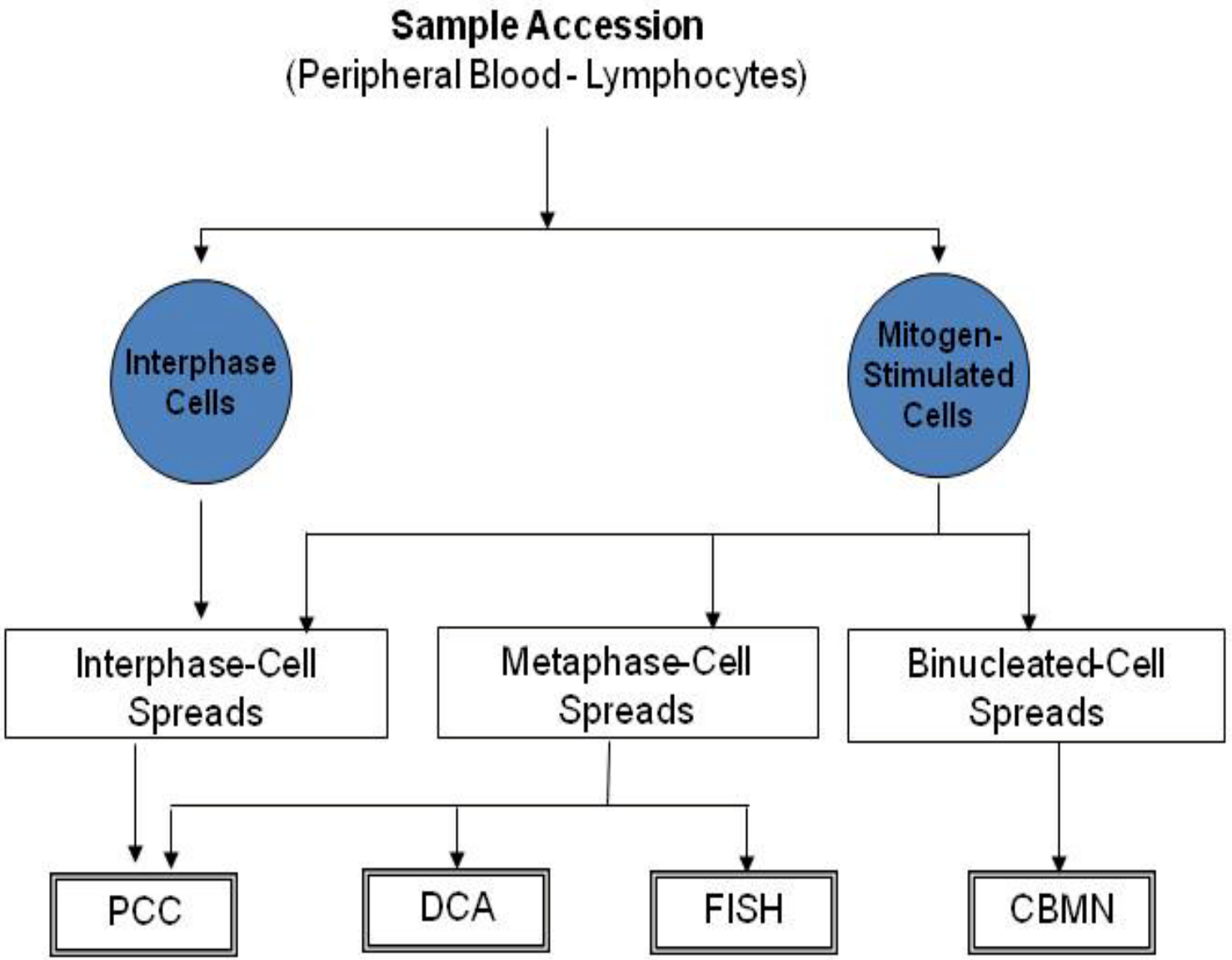
Assessment Method	Parameters for considering assessment method for use in early (<5 d) triage screening			Applicable for scoring ARS severity	Dose (Gy) or ARS response category level to select for priority cytogenetic triage analysis	
	Time for analysis	Estimate cost per sample, US Dollars			Triage dose, Gy	Response category levels
Direct Recording of Location History	< 2 min	-			3-7	
Direct Observation of Clinical Signs and Symptoms	< 5 min	-		Yes	3-7	1-4
Personal Monitoring (Direct, non invasive)						
- *in vivo* EPR	Unknown	Unknown			3-7	
- portable hand held meters (triage/screening)	< 5 min	-			-	
- portal monitors (triage/screening)	< 2 min	-			-	
- whole-body counting	> 25 min	-			-	
Personal Monitoring (Indirect, invasive)		**Detection limit,#**	**Estimate cost per sample, US Dollars#**			
- blood chemistry **Amylase activity, CRP, etc.**	< 3 min		<$2	**Yes**	3-7	
- CBC and differential/lymphocyte count	< 2 min		<$1	Yes	3-7	1-4
- *in vitro* EPR (i.e., nails)	<15 min		Unknown		3-7	
- nasal swab	> 1 d	50 pCi/swab	$70		-	
- stool sample	> 1 d	5 pCi/g	$80		-	
- urine sample (spot; 24-hr)	< 1 d; > 1 d	30 pCi/vial	$90		-	
- cytogenetics (i.e., 20-50 metaphase triage; 1000 metaphase analysis)	>3 days	1 Gy; 0.2 Gy	Unknown; $500-3,000		-	
Area Monitoring						
- dosimetry results (*e.g.* TLDs, aerial measurements) combined with personal location information	Unknown	-			3-7	

*The Table was modified a version reported by Alexander and colleagues [2].

Note that the personal and area monitoring methods are listed in alphabetical order and, therefore, their location in the table does not infer priority or preference.

Radiobioassay detection limits and costs are based on ^{137}Cs isotope and 1 min gamma-ray spectrometry analysis with high priority count (costs 3-times routine) with no automatic sample changers used. Detection limits for cytogenetic analysis are presented in acute photon equivalent dose in units of Gy.

Blakely WF (2008) Early Biodosimetry Response: Recommendations for Mass-Casualty Radiation Accidents and Terrorism. Refresher Course for the 12th International Congress of the International Radiation Protection Association, October 19–24, 2008, Buenos Aires, Argentina, accessible at website: http://www.irpa12.org.ar/PDF/RC/_12_fullpaper.pdf

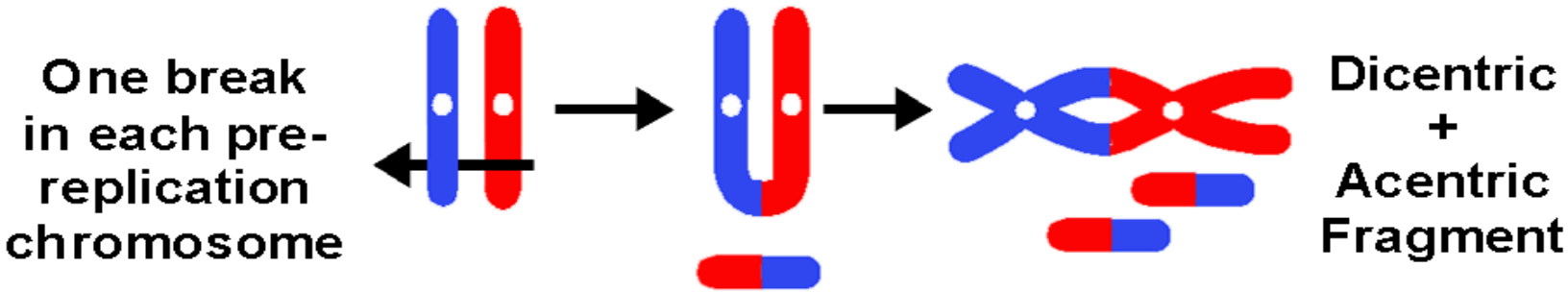


Types of Assay:	Premature Chromosome Condensation	Dicentric (and ring) Chromosom e Abberation	Fluorescence In Situ Hybridization	Cytokinesis Blocked Micronuclei

	Cytogenetic Chromosome Aberration Assays			
	Premature chromosome condensation (**PCC**) assay	Dicentric (and ring) chromosome aberration (**DCA**) assay	Fluorescent *in situ* hybridization (**FISH**) translocation chromosome aberration (**Translocation**) assay	Cytokinesis block micronucleus (**CBMN**) assay
Typical aberrations scored for biodosimetry applications	excess chromosome fragments dicentrics* (and rings) translocations*	dicentrics (and rings)	dicentrics* (and rings) translocations*	micronuclei
Typical radiation scenario applications	acute (including high doses)	low-level acute protracted prior exposure	protracted prior exposure	acute
Photon equivalent, acute dose range (Gy) for whole-body dose assessment	0.2 to 20	0.1 to 5	0.25 to 4	0.3 to 5
Useful for partial-body exposure applications	Yes	Yes	NA[#]	NA
Useful for triage dose assessment	Yes	Yes	NA	Yes
Standardization of assay	NA	ISO standard for reference assay (1,000 metaphase spreads or 40 dicentrics) ISO standard for triage assay (20-50 metaphase spreads) - pending	NA	ISO standard for reference assay - pending

Table modified from TMT Handbook [73]

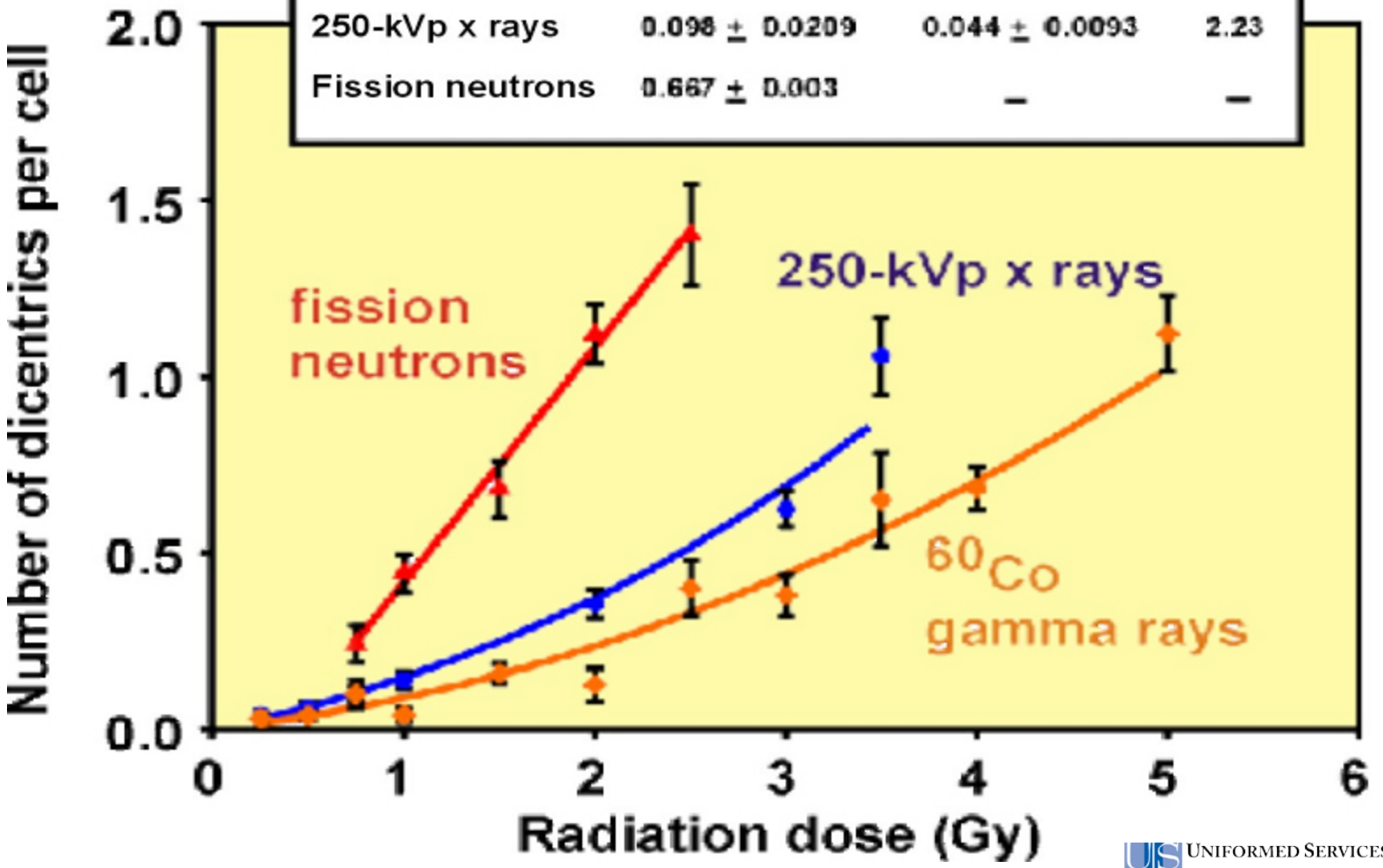
Lymphocyte Metaphase Spread Dicentric Assay



The dicentric assay has been validated and used for dose assessment in occupational and accidental exposure scenarios since it was introduced by Dr. M. Bender in 1964.

The coefficients α and β with estimates of SE for dicentric calibration curves

Radiation type	$\alpha \pm$ SE(Gy^{-1})	$\beta \pm$ SE(Gy^{-2})	α/β
60Co gamma rays	0.059 ± 0.0136	0.029 ± 0.0046	2.03
250-kVp x rays	0.098 ± 0.0209	0.044 ± 0.0093	2.23
Fission neutrons	0.667 ± 0.003	–	–



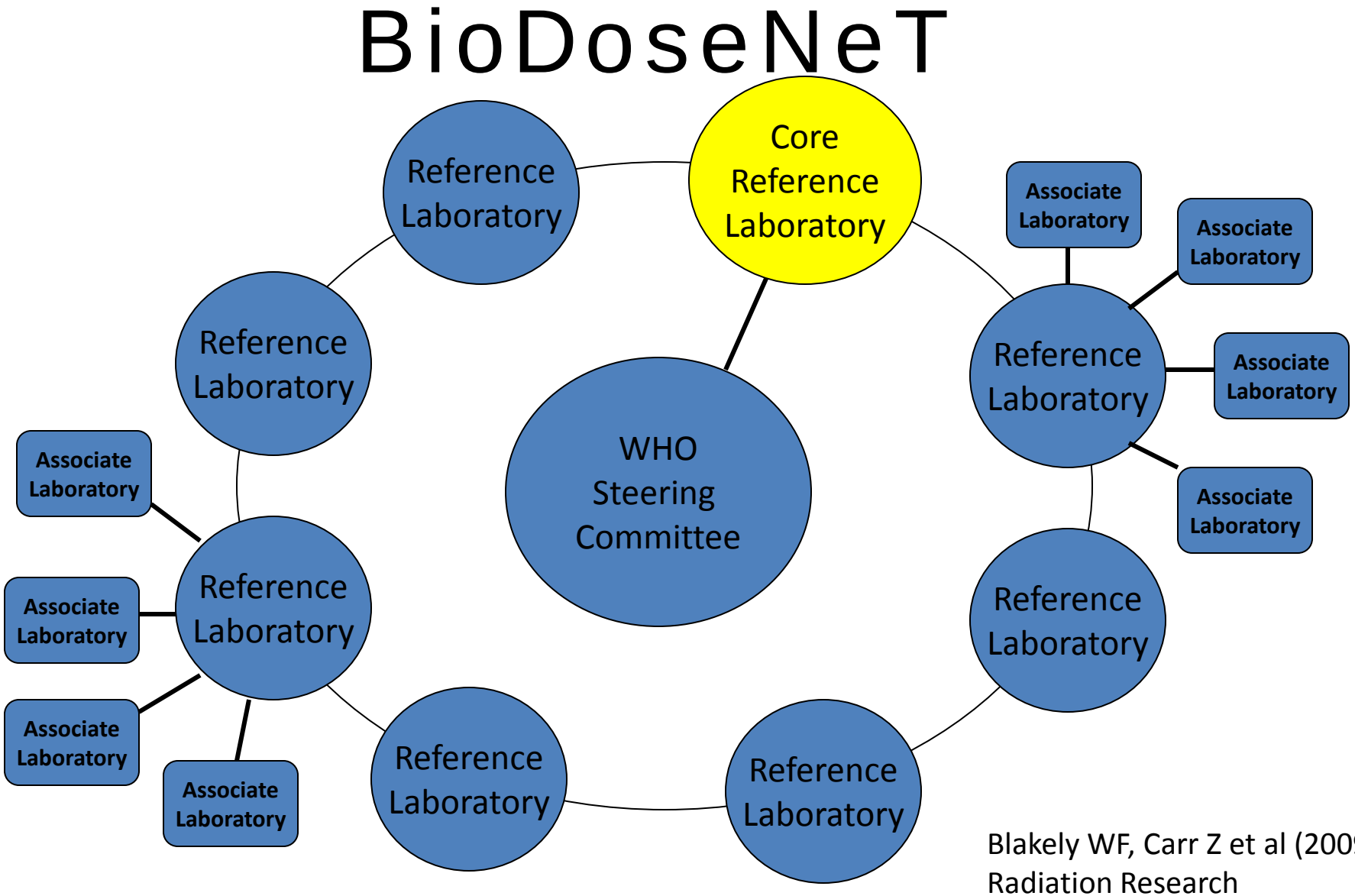
Uniformed Services University
of the Health Sciences
Armed Forces Radiobiology Research Institute

Strategies to Enhance Rapid Throughput for Cytogenetic Biodosimetry

- National expert cytogenetic biodosimetry laboratories
  - REAC/TS; AFRRI (USA)
- Triage and/or dicentric chromosome aberration (DCA) QuickScan scoring
  - Lloyd (UK); Wilkins (Canada)
- Use of commercial off-the-shelf automation devices (metaphase harvesters, metaphase spreaders, metaphase finders) and automated scoring
  - Prasanna, Ramakumar, and colleagues (AFRRI)
  - Romm and colleagues (Germany)
- An internet-based strategy to score digitized electronic images
  - Livingston (REAC/TS)
- Development of a network of reference and supplementary national and international cytogenetic biodosimetry laboratories
  - UK/France/Germany; Japan; Canada; USA; Latin America; South Korea

WHO Consultancy on BioDoseNet development – 17-18 December 2007

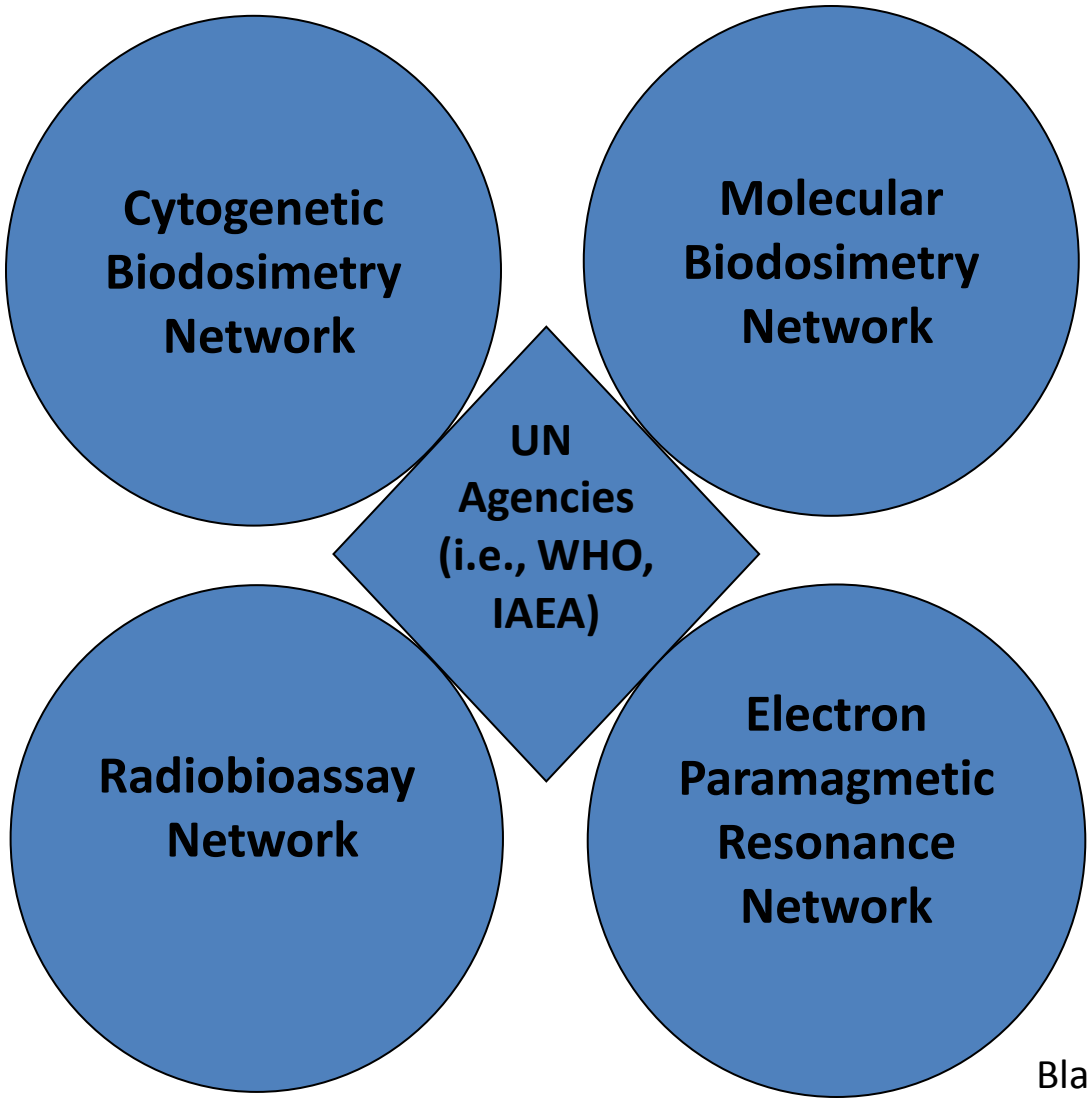
World Health Organization



Blakely WF, Carr Z et al (2009) Radiation Research 171(1):127–139

WHO's Network of Expert Reference Laboratories for Dose Assessment

World Health Organization



Blakely WF, Carr Z et al (2009) Radiation Research 171(1):127–139

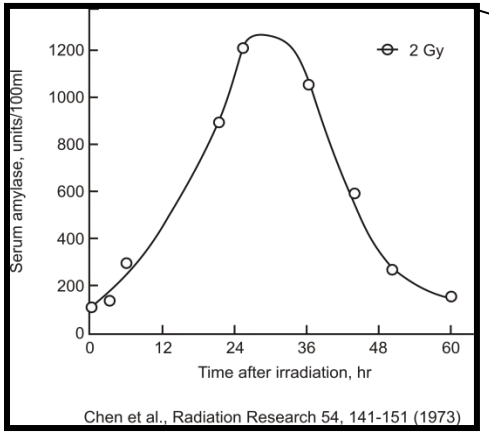
Candidate radiation biomarkers and functional tests from various tissue system or organs

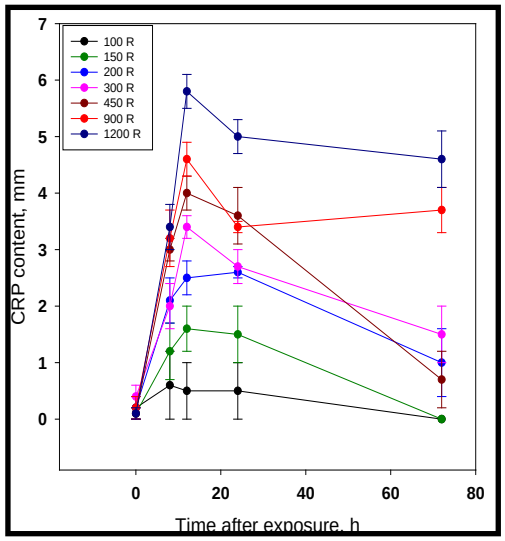
Tissue system or organ	Candidate radiation biomarker	Candidate radiation bioindicator or functional test	Radiation pathology	Reference
Gastrointestinal (GI) or Digestive System				
Parotid salivary gland	Amylase activity	↑ Serum or urinary amylase activity	Mucositis	Chen et al. 1973; Hofmann et al. 1990; Dubray et al. 1992; Becciolini et al. 2001; Blakely et al. 2007; Blakely et al. 2010
Small intestine	Citrulline, neurotension and gastrin hormones	↓ Serum or plasma citrulline, neurotension or gastrin; ↑ sugar concentration ratios using dual-sugar permeability test measured in serum	GI ARS subsyndrome	Lutgens et al. 2003, 2004; Vigneulle et al. 2002; Dublineau et al. 2004; Bertho et al. 2008
Liver	C-reactive protein (CRP); Serum amyloid A (SAA) Oxysterol 7a-hydroxycholesterol	↑ Serum or plasma CRP or SAA; ↑ Plasma oxysterol 7a-hydroxycholesterol	ARS subsyndrome; Hepatic tissue radiation injury	Mal'tsev et al. 1978, 2006; Goltry et al. 1998; Koc et al. 2003; Roy et al. 2005; Ossetrova et al. 2007; 2010; Ossetrova and Blakely 2009; Blakely et al. 2010;
Hemopoietic System				
Bone marrow	Flt-3 ligand (Ftl-3), IL-6, G-CSF	↑ Serum or plasma Flt-3	Bone marrow ARS subsyndrome	Bertho et al. 2001, 2008
Cutaneous System				
	Cytokines (IL-1, IL-6, tumor necrosis factor, GM-CSF, TGF-β, intracellular adhesion molecule, MMP	↑ IL-1, IL-6, GM-CSF, TGF- β, intracellular adhesion molecule, and MMP measured from skin tissues	Cutaneous ARS subsyndrome	Martin et al. 1997; Ulrich et al. 2003; Liu et al. 2006; Muller and Meineke 2007; Guipard et al. 2007
Respiratory System				
Lung	Oxysterol 27-hydrocholesterol	↑ plasma oxysterol 27-hydrocholesterol	Respiratory ARS subsyndrome	Roy et al. 2005
Cerebrovascular/Central Nervous System				
	Oxysteril 24S-hydroxycholesterol	↑ plasma oxysteril 24S-hydroxycholesterol	Cerebrovascular ARS subyndrome	Roy et al. 2005

Radiation Protein Biomarker Concept

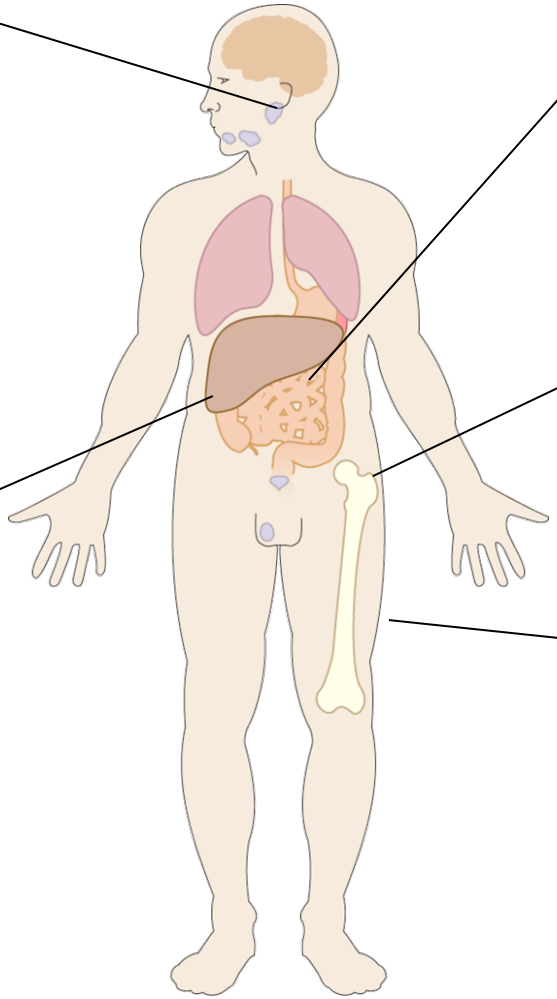
Time Course

Acute Injury Biomarkers

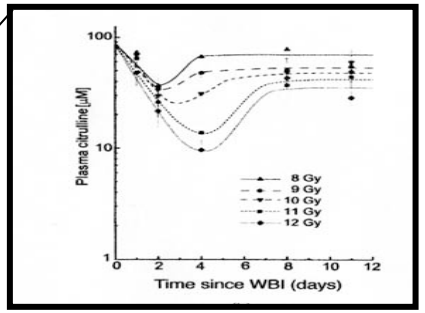




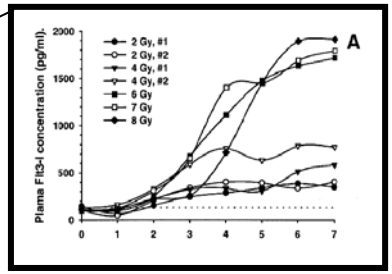
Maltsev *et al.*, [Report of Russian Academia of Sciences] 239(3): 750-2, 1978 (in Russian).



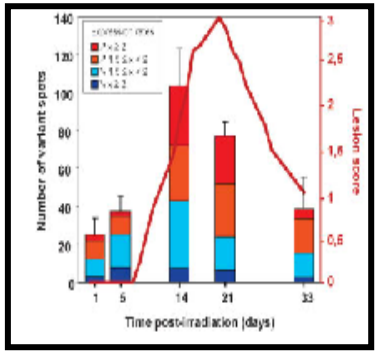
ARS Organ Injury Biomarkers



Lutgens *et al.* IJROBP 57(4): 1067, 2003



Bertho *et al.* IJRB 77(6): 703-712, 2001

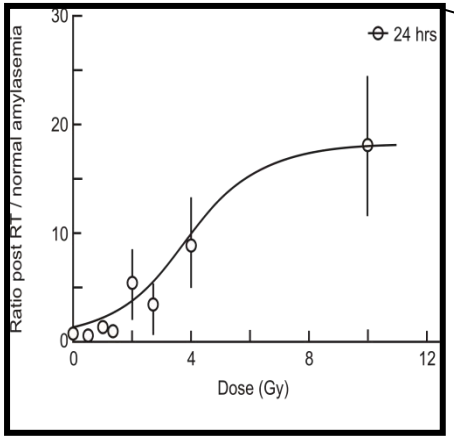


Guipaud et al. Proteomics 7: 3392-4002, 2007

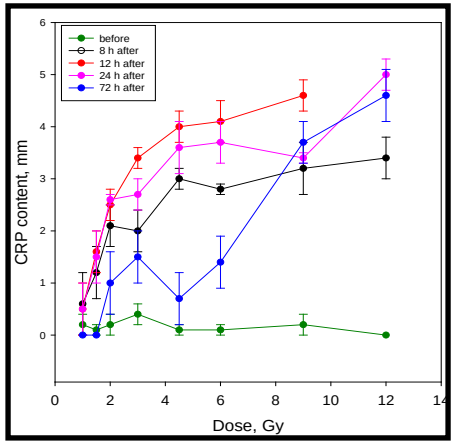
Radiation Protein Biomarker Concept

Dose Response

Acute Injury Biomarkers



Dubray *et al.*, Radiother. Oncol. 24(1):21-6, 1992



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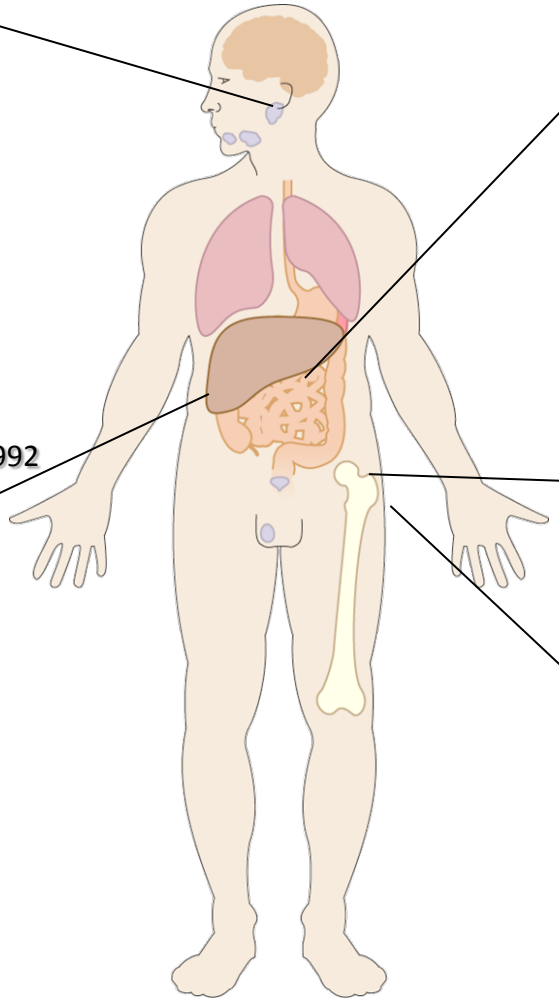
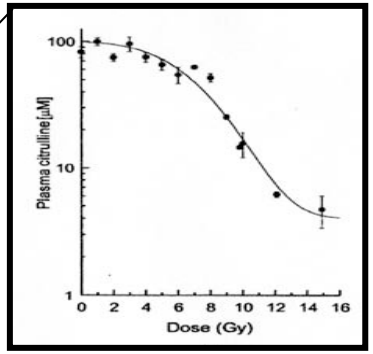
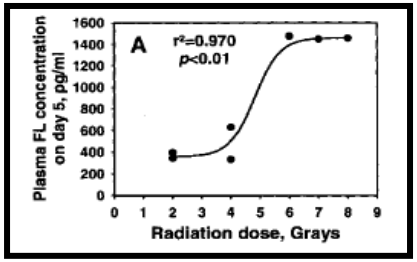


ARS Organ Injury Biomarkers



Lutgens *et al.* IJROBP 57(4): 1067, 2003



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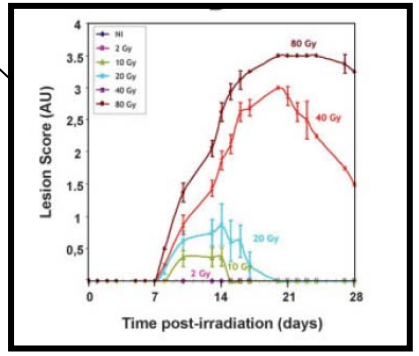

Guipaud et al. Proteomics 7: 3392-4002, 2007

Select list of radiation-responsive blood based proteomic, metabolomic, and hematology biomarkers showing their dose range (for various models) and time-window for meaningful diagnosis of radiation injury and dose*

Proposed blood or serum biomarker	Pathways	Dose range (Gy)				Time window for meaningful diagnostics	References
		Rodent studies	NHP studies	Human radiation therapy	Human radiation accidents		
Salivary α-amylase activity	Parotid gland tissue injury	NA	0–8.5 Gy	0.5–10 Gy	3.5, 8, and 18 Gy (Tokai-mura)	12–36 h; peaks at 24 h	Hofmann et al. 1990; Dubray et al. 1992; Becciolini et al. 2001; Blakely et al. 2007; Blakely et al. 2010
IL-6, G-CSF	Immunostimulatory effects on bone marrow cells	1–7 Gy	6.5 Gy	NA	1–10 Gy	4–48 h; 3-8 d	Beetz et al. 1997; Gartel et al. 2002; Bellido et al. 1998; Ossetrova et al. 2007, 2009
Flt-3 ligand	Bone marrow aplasia	1–7 Gy	2-8 Gy	NA	0.25 to 4.5 Gy	24 h–10 d	Bertho et al. 2001; Bertho et al. 2008
CRP, SAA	Acute-phase reaction	1–7 Gy (SAA)	1–14 Gy (CRP)	1–20 Gy (CRP)	1–10 Gy (CRP)	6 h–4 d; 5-14 d	Mal'tsev et al. 1978, 2006; Koc et al. 2003; Goltry et al. 1998; Ossetrova et al. 2007, 2010; Ossetrova and Blakely, 2009; Blakely et al. 2010
Citrulline	Small bowel epithelial injury	1–14 Gy	Not done	1–20 Gy (2-Gy daily fractions)	~4.5 Gy	>24 h	Lutgens et al. 2003, 2004; Bertho et al. 2008
Lymphocytes, neutrophils, and ratio of neutrophils to lymphoyctes	Hematopoietic tissue injury	1–7 Gy	1–8.5 Gy	1–20 Gy	0–30 Gy	2 h–8 d	Goans et al. 1997; Guskova et al. 1997; Blakely et al. 2005, 2007; Ossetrova et al. 2010

*Concept to use of multiple biomarkers for radiation injury and dose assessment (Blakely, Ossetrova et al., U.S. Patent Application No. 60/812,596.)

“Because of recent terrorist activities and intelligence information, there is strong sentiment that it is not a question of if, but when, a radiological or nuclear attack will occur.”

W. Craig Conklin (Department of Homeland Security) and CDR Philip L. Liotta (Armed Service Medical Intelligence Command)

“If you fail to plan, you plan to fail.”